REMARKS

The current application relates to a container comprising an immunologically isolated genetically altered bone marrow stromal cell. Claims 69, 70, 97-108, 112, and 113 are currently pending in the above-referenced application. Claims 1-36 and 39-54 have been withdrawn as being drawn to non-elected inventions and claims 37, 38, 55-68, 71-96 and 109-111 were canceled in previously filed Amendments. Therefore, claims 69, 70, 97-108, 112, and 113 are currently under consideration.

Claims 69 and 112 have been amended herein to recite that the first and the second expressible gene is under the control of a different promoter. Support for the amendment to claims 69 and 112 is found throughout the as-filed specification as fully set forth below. As such, no new matter has been added by way of the present Amendment. Further, claim 113 has been amended herein as suggested by the Examiner in order to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Rejection of claim 113 under 35 U.S.C. §112, second paragraph

Claim 113 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner asserts that the recitation of "the protein" is unclear as to which of the two proteins as recited in the base claim the term "the protein" refers to. Accordingly, Applicants have amended claim 113 to recite "**said** protein," as suggested by the Examiner on page 3 of the present Office Action in order to distinguish the protein from the "cytotoxic protein."

Therefore, Applicants respectfully submit that claim 113 as amended is not indefinite, and hereby request that the rejection under 35 U.S.C. §112, second paragraph be reconsidered and withdrawn.

Rejection of claims 69-70, 97-108, 112 and 113 under 35 U.S.C. §103(a)

The Examiner has rejected claims 69-70, 97-108, 112 and 113 pursuant to 35 U.S.C. § 103(a) as being *primia facie* obvious over Gerson (U.S. Pat. No. 5,591,625) in view of any one of Naughton et al. (U.S. Pat. No. 5,858,721), Caplan et al. (U.S. Pat. No. 5,197,985), Schinstin et al. (U.S. Pat. No. 5,843,431), Mardon (1987, Cell Tissue Res. 25:157-165), and the as-filed specification. Specifically, the Examiner opines that Gerson teaches the use of

genetically modified mesenchymal stem cells (MSCs), wherein the MSCs are contained in a porous ceramic cube device. Not wishing to be bound to any particular theory, but rather for consistency in this Amendment, mesenchymal stem cells will be referred herein as bone marrow stromal cells (BMSCs), as these cells are recognized in the art as being the same. The Examiner also asserts that the secondary references teach the use of a microcarrier, a diffusion chamber or a microcapsule to enhance the delivery and subsequent release and differentiation of the implantable cell to the target site. Further, the Examiner indicates that the specification discloses well know technologies and devices for immunological isolation means such as, but not limited to a diffusion chamber. Therefore the Examiner reasons that it would have been *prima facie* obvious for one skilled in the art at the time of the invention to combine Gerson et al. with the teachings of the secondary references and the as-file specification to arrive at the present invention. Applicants respectfully traverse the rejection for the following reasons.

The three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP § 2142

The first prong of the *In re Vaeck* test, the requirement that the references themselves or the knowledge in the art must provide some suggestion or motivation, has not been met in this instance. The Examiner points to various sections in Gerson et al. to demonstrate a genetically modified BMSCs wherein the cells are transduced by a retroviral vector expressing more than one protein, which proteins include a cytotoxic protein (thymidine kinase) and a secretory antibiotic resistant protein. Applicants agree with the Examiner that Gerson teaches a genetically modified BMSCs. However, Applicants respectfully contend that Gerson does not

teach a genetically modified BMSC as recited in the pending clams. That is, claim 69 and 112 relate to a bone morrow stromal cell comprising a first expressible gene construct and a second expressible gene construct encoding a cytotoxic protein. Nowhere does Gerson teach or suggest a first and second expressible gene construct. Gerson merely lists various genes that may be used to genetically modify BMSCs, wherein thymidine kinase (a cytotoxic protein) is included in the list. Applicants are of the opinion that the Examiner has overlooked a feature of the present invention in that the bone marrow stromal cell comprises a second expressible gene construct encoding a cytotoxic protein. Again, nowhere does Gerson teach or suggest this feature.

Applicants respectfully point out that the Examiner has inappropriately referenced various sections of Gerson et al. to support the rejection of the pending claims under 35 U.S.C. § 103(a). That is, the Examiner points to column 9, lines 5-8; column 10, lines 3-9; column 11, lines 30-51; column 12, lines 14-47; and column 14, first paragraph to demonstrate that Gerson teaches an aspect of the present invention. However, Applicants do not agree that Gerson teaches or suggests the present invention of an implantable container containing an isolated BMSC transduced with more than one protein. That is, column 9, lines 5-8 merely discloses that the cells can be implanted alone or in the context of a porous ceramic cube device. Nowhere does column 9 teach the present invention. Further, column 10 discloses that the cells can be engineered to express cytotoxic genes such as thymidine kinase. Again, as discussed elsewhere herein, there is no reference to the cytotoxic gene being a second expressible gene construct, not to mention that there is also no suggestion that Gerson's cells are isolated from immune cells.

With respect to the Examiner's reference to columns 11 and 12 to demonstrate a vector expressing more than one protein, Applicants contend that the subject matter as set forth in columns 11 and 12 should not be applied to support the rejection of the pending claims under 35 U.S.C. § 103(a) as being *prima facie* obvious. That is, columns 11 and 12 do not teach or suggest a second expressible gene construct encoding a cytotoxic protein, nor do they teach or suggest the expression of these vectors in BMSCs. Rather, columns 11 and 12 teach NIH-3T3 cells co-electroporated with a three plasmid transfection system, wherein none of the three plasmids is a cytotoxic gene. Specifically, columns 11 and 12 disclose the introduction of three plasmids in NIH-3T3 cells, the first plasmid containing the retroviral sequences for gag and pol; the second plasmid containing nucleic acid sequences for the amphotropic envelope protein; and

the third plasmid containing the nucleic acid sequence for the hygromycin gene. Again, the disclosure set forth in columns 11 and 12 cannot render the present invention obvious.

The Examiner references column 14 in Gerson to provide support that Gerson teaches BMSCs transduced by a retroviral vector expressing more than one proteins. Applicants respectfully contend that the disclosure set forth in column 14 does not teach a first expressible gene construct encoding a protein and a second expressible gene construct encoding a cytotoxic protein. That is, column 14 teaches the transduction of BMSCs using retroviruses, wherein BMSCs are incubated with retroviral supernatant from AM-12PNL2 cells which contain the retrovirus vM5neolacZ. As described in Example 1, vM5neolacZ retroviral vector was constructed to have sequences of the long terminal repeats (LTRs) drive transcription of the Tn5 neogene and the lacZ gene. Therefore, Gerson merely teaches the expression of two recombinant genes and neither of these genes is a cytotoxic gene. As such, one skilled in the art would recognize that Gerson simply teaches a method of genetically modifying BMSCs and methods of accessing the efficacy of gene transduction and expression of both the neomycin and lacZ genes. The disclosure of Gerson does not teach that the transduced BMSCs would have a therapeutic use nor does it teach or suggest Applicant's cell. Certainly, the specification of Gerson does not provide any guidance as to how one skilled in the art might arrive at the present invention as set forth in the pending claims. A mere hint that BMSCs can be genetically modified is not enabling and cannot be considered a "teaching or suggestion" of a first expressible gene construct encoding a protein and a second expressible gene construct encoding a cytotoxic protein within the meaning of 35 U.S.C. §103(a).

As discussed elsewhere herein, Gerson does not teach or suggest the present invention. However for argument purposes, in the event that Gerson did somehow teach or suggest a second expressible gene construct encoding a cytotoxic protein, Applicants have amended claims 69 and 112 herein to recite that the first and the second expressible gene is under the control of a different promoter. Applicants assert that the amendment to claims 69 and 112 regarding promoters in no way should be construed that Applicants agree with the Examiner that Gerson teaches a second expressible gene construct encoding a cytotoxic protein, but rather is a good faith effort to expedite the prosecution of the present application. Support for the amendment to claims 69 and 112 is found throughout the as-filed specification. For example, Figure 1 illustrates that the first expressible gene is driven by the LTR promoter while the second

gene is under the control of the CMV promoter. Figure 1 also demonstrates that desired genes for transfection into BMSCs can also be operably linked to the human procollagen promoters. As such, no new matter has been added by way of the present Amendment. Applicants point out that Figure 1 in Gerson et al. discloses that the expression of lacZ and the neomycin gene is under the control from one promoter which further teaches away from the present invention as recited in the presently amended claims.

Applicants assert that the present invention is far too big a leap from what is taught in the Gerson specification. One of skill in the art would not have been motivated in any way to combine Gerson with any of Naughton et al., Caplan et al., Schinstin et al. or Mardon because one of skill in the art would appreciate that the invention in Gerson is merely a disclosure of genetically modified bone marrow stromal cells. There is nothing in Gerson that would compel one of skill in the art to combine what is taught in Gerson with the methods of delivering a cell to an animal in vivo (i.e., the methods of using microcarriers, diffusion chambers, etc.) because Gerson does not teach or suggest delivery of a transfected bone marrow stromal cell to an animal, wherein the transfected bone marrow stromal cell expresses a first protein and a second cytotoxic protein, and further wherein the first and second expressible gene is under the control of a different promoter.

The Examiner cited Naughton et al., Caplan et al., Schinstin et al. and Mardon as indicative of the state of the art with regard to delivery systems for cells (diffusion chambers, microcarriers, etc.), but these references do not in and of themselves render the present invention obvious. Because neither of Naughton et al., Caplan et al., Schinstin et al. or Mardon (more fully discussed below) do not overcome the deficiencies of Gerson. These references (1) do not teach or suggest a genetically modified bone marrow stromal cell expressing a first protein and a second cytotoxic protein, and further wherein the first and second expressible gene is under the control of a different promoter and (2) do not motivate one of skill in the art to combine any them to arrive at the present invention.

In the Examiner's view, the secondary references Naughton et al., Caplan et al., Schinstin et al. and Mardon all disclose the availability of microcarriers, diffusion chambers, and microcapsules as delivery methods for bone marrow stromal cells. Applicants contend that because none of the secondary references corrects the deficiencies of Gerson, the Examiner has not met his burden of proving a *prima facie* case of obviousness.

As discussed elsewhere herein, one of the deficiencies in Gerson is that the reference does not teach Applicants' cells. Neither Naughton et al., Caplan et al., Schinstin et al. nor Mardon overcomes that deficiency. Naughton discloses the establishment of a three-dimensional cell culture system which can be used to culture a variety of different cells and tissues *in vitro* for prolonged periods of time. Nowhere does Naughton teach the cells of the present invention as recited in the claims following entry of the present Amendment. As such, the teachings of Naughton do not correct the deficiencies of Gerson. Therefore, Applicants submit that Naughton, combined with Gerson, does not constitute a *prima facie* case of obviousness.

Caplan discloses methods of adhering cells to a container, which is then implanted into defective skeletal tissue, for example, so that the cells can proliferate into bone tissue. Applicants submit that the cells in Caplan are not genetically altered in any way. In addition, in some aspects of the invention in Caplan, the cells are ultimately induced to differentiate into bone-forming cells within the diffusion chamber or the ceramic graft. Applicants' cells serve to continuously provide a protein to the host animal.

Further, Applicants contend that Caplan teaches away from the present invention in at least one aspect. In Caplan, diffusion chambers containing mesenchymal cells, which cells were physically isolated from the immune cells of the host animal were compared with porous ceramic carriers grafted with mesenchymal cells, which cells were not physically isolated from the immune cells of the host animal, in their ability to produce bone or cartilage (see column 12, line 57-column 13, line 5 and column 13, line 43-60). The data in Caplan indicated that bone/cartilage formation was not observed in any experiment using the diffusion chamber. Bone formation was observed and reproduced using the ceramic graft carrier (see column 13, lines 6-30). Therefore, Applicants contend that results demonstrating lack of bone production from the cells which are isolated from the cells from the host animal's immune system teach away from the present invention.

Applicants note that claims 69 and 112 of the present application require the limitation that bone marrow stromal cells in the container be isolated from the cells of the host animal's immune system. The data in Caplan supports the opposite situation. The cells that were not isolated from the host animal's immune system (i.e., on the ceramic graft) produce bone; the cells that were isolated did not produce bone. Therefore, one of skill in the art would

not be motivated to isolate cells from the host animal's immune system (i.e., in the diffusion chamber), because they do not serve their intended purpose which, in Caplan, is to produce bone. For these reasons, Applicants submit that Caplan, combined with Gerson, does not offer a *prima facie* case of obviousness.

The Mardon reference also does not correct the deficiency in Gerson. Mardon does not teach or suggest the cells of Applicants' invention. Rather, Mardon teaches placing a mixture of marrow cells in a diffusion chamber for implantation in an animal (see page 158). The cells in the present invention are isolated by a method similar to the method used in Mardon, but with the additional step of culturing the cells for a period of time and discarding those cells which do not adhere to the culture dish (see for example, paragraph bridging page 36 and 37 of the present specification).

Further, the cells in Mardon are not genetically altered in any way. The cells in Mardon are a mixture of adherent and nonadherent cells isolated from the bone marrow of rats. The purpose of the experiment in Mardon was to determine whether that mixture of cells had any osteogenic potential when implanted within a diffusion chamber into a rat. There is no suggestion in Mardon that the mixture of bone marrow cells used in the experiments could be genetically altered and implanted to provide a protein to a rat or any other animal in need of the protein. Mardon does not correct the deficiency in Gerson to define Applicants' cells, and further, does not teach or suggest use of a diffusion chamber in conjunction with Applicants' cells.

Applicants are still unclear as to the relevance of the Schinstin reference as it pertains to the present invention. First, Schinstin does not overcome the deficiency of Gerson to teach the cells of Applicants' invention. Schinstin also does not teach or suggest use of a container containing bone marrow stromal cells, which cells are physically isolated from the immune cells of the animal in which the container is implanted, to provide a protein to an animal in need of the protein.

Second, while Schinstin discusses use of microcarriers previously known in the art in order to enhance or inhibit cell proliferation, the microcarriers disclosed in Schinstin do not physically isolate the cells adhered to the microcarrier from the host animal's immune system. Without more, this reference cannot contribute to a *prima facie* case of obviousness.

None of Naughton et al., Caplan et al., Schinstin et al. or Mardon overcomes the deficiency in Gerson to teach or suggest Applicants' cells. Further, neither of Naughton et al., Caplan et al., Schinstin et al. or Mardon supports the claim language of claim 69 and 112, in which the container physically isolates the bone marrow stromal cells of the present invention from the host animal's immune system. For all of these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 69, 70, 97-108, 112, and 113 under 35 U.S.C. §103(a).

The second prong of the *In re Vaeck* test, the requirement that there be a reasonable expectation of success, is similarly not met in this instance. As detailed above, Gerson merely discloses genetically modified BMSCs, and does not teach or suggest a first and second expressible gene construct wherein the second expressible gene construct is a cytotoxic gene, and further wherein the first and second expressible gene construct is under the control of a different promoter. One skilled in the art would understand that the disclosure set forth in Gerson, specifically the list of genes able to be used to genetically modify BMSCs, cannot be used to arrive at Applicants' invention. That is, without further information, which Gerson does not provide, one of skill in the art has no expectation of success in generating the cells of the present invention. If the skilled artisan were to follow the teachings of Gerson and attempt to generate the cells of the present invention, the skilled artisan would obtain a cell that expresses more than one recombinant protein. However, the cell would not encompass a second protein wherein the second protein is a cytotoxic protein, and further the two recombinant proteins expressed from the BMSC would not have been under the control of a different promoter. Therefore, there would have no expectation of success to arrive at Applicants invention based on the teachings of Gerson.

As noted above, none of Naughton et al., Caplan et al., Schinstin et al. or Mardon overcomes the deficiency in Gerson to teach or suggest Applicants' cells. That is, none of these references teach a genetically modified bone marrow stromal cell, wherein the cell expresses a first protein and a second cytotoxic protein, and further wherein the first and second expressible gene is under the control of a different promoter. Therefore, the skilled artisan has no reasonable expectation of success in arriving at the present invention.

In addition to the requirements set forth above, in order to establish a *prima facie* case of obviousness, the prior art reference(s) must teach or suggest all of the claim limitations.

Similar to the other prongs of the *In re Vaeck* test, Gerson in view of either Naughton et al., Caplan et al., Schinstin et al. or Mardon fail to teach or suggest all of the claim limitations. Applicants respectfully contend that as discussed elsewhere herein, the cited references, whether alone or in combination, do not teach all of the claim limitations. Gerson does not teach Applicants' cell. Further, Naughton et al., Caplan et al., Schinstin et al. or Mardon also does not teach the invention as discussed in detail elsewhere herein. When one takes Gerson with either Naughton et al., Caplan et al., Schinstin et al. or Mardon, one also does not arrive at the present invention. This is because, as stated above, each of these references is fatally deficient with respect to the present invention and none are capable of correcting the deficiencies of the others.

For all of the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection of claims 69, 70, 97-108, 112, and 113 under 35 U.S.C. §103(a).

With respect to the Examiner's rejection of claims 69-70, 97-108, 112 and 113 pursuant to 35 U.S.C. § 103(a) as being *primia facie* obvious over Gerson in view of the as-filed specification, Applicants assert that the combination of Gerson with Applicants' own disclosure cannot support a case of *prima facie* case of obviousness. That is, the MPEP states, in relevant part:

> The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP § 2143

As such, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection of claims 69, 70, 97-108, 112, and 113 under 35 U.S.C. §103(a) with respect to the combination of Gerson with Applicants own disclosure.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 69, 70, 97-108, 112, and 113 are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

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(Date)

By: _____

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Enclosure: Petition for Extension of Time and fee therefor